

PERSISTENT ANTERIOR THORACALGIA IN A PATIENT WITH MEDIASTINAL - PULMONARY SARCOIDOSIS

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Abstract

Sarcoidosis is a systemic condition characterized by the formation of non-caseating granulomas in any organ or tissue, with a predominant impact on the lungs and intrathoracic lymph nodes⁽¹⁾. The heterogeneity of the disease is reflected in the broad possibilities of the clinical and paraclinical evolution, which can range from the incidental identification of the disease in an asymptomatic patient to the progressive chronic involvement of the affected organs. Commonly, sarcoidosis initially manifests through nonspecific respiratory symptoms, characterized by dry cough, dyspnea, chest pain, and fatigue^(2,3). Generally, it is considered that this condition occurs in individuals with a susceptible genetic background, exposed to certain environmental factors or antigens that remain unknown, despite numerous existing hypotheses⁽⁴⁾.

Cardiac involvement in sarcoidosis has a significant negative impact on prognosis. Although this location of the disease is predominantly silent, 5% of cases present with dilated or restrictive cardiomyopathy, progressive heart failure, high-grade atrioventricular blocks, and ventricular arrhythmias⁽⁵⁾.

The authors present the case of a young patient who, although at the onset of the disease, exhibited a typical clinical and imaging profile of sarcoidosis, myocardial involvement - a rare localization of this pathology - was detected during the course of the condition. Patients with sarcoidosis may have normal spirometry, may present with a restrictive syndrome (similar to diffuse interstitial lung diseases), or an obstructive syndrome, secondary to the involvement of small bronchi and bronchial distortions caused by the disease, often with an unfavorable prognosis.

Keywords: Sarcoidosis, cardiac sarcoidosis, mediastino-pulmonary form, diagnosis.

Rezumat

Sarcoidoza este o afecțiune sistemică caracterizată prin formarea de granuloame necazeoase în orice organ sau țesut, cu impact predominant asupra plămânilor și ganglionilor limfatici intratoracici⁽¹⁾. Heterogenitatea bolii se reflectă în posibilitățile largi de evoluție clinică și paraclinică, care pot varia de la identificarea accidentală a bolii la un pacient asimptomatic, până la implicarea cronică progresivă a organelor afectate.



INTERNAL MEDICINE

Clinical Cases

De obicei, sarcoidoza se manifestă inițial prin simptome respiratorii nespecifice, caracterizate prin tuse uscată, dispnee, dureri toracice și oboseală^(2,3). În general se consideră că această afecțiune apare la indivizi cu un fond genetic susceptibil, expuși la anumiți factori de mediu sau antigene care rămân necunoscute, în ciuda numeroaselor ipoteze existente⁽⁴⁾.

Implicarea cardiacă în sarcoidoză are un impact negativ semnificativ asupra prognosticului. Deși această localizare a bolii este predominant silențioasă, 5% dintre cazuri prezintă cardiomiopatie dilatativă sau restrictivă, insuficiență cardiacă progresivă, blocuri atrioventriculare de grad înalt și aritmii ventriculare⁽⁵⁾.

Autorii prezintă cazul unui pacient tânăr care, deși la debutul bolii, a prezentat un profil clinic și imagistic tipic de sarcoidoză, afectarea miocardică - o localizare rară a acestei patologii - fiind fost depistată pe parcursul evoluției bolii. Pacienții cu sarcoidoză pot prezenta spirometrie normală, pot prezenta un sindrom restrictiv (asemănător bolilor pulmonare interstițiale difuze), sau un sindrom obstructiv, secundar implicării bronhiilor mici și distorsiunilor bronșice cauzate de boală, de multe ori cu prognostic nefavorabil.

Cuvinte cheie: sarcoidoză, sarcoidoză cardiacă, formă mediastino-pulmonară, diagnostic.

Introduction

Sarcoidosis is a systemic disease of unknown etiology, histologically characterized by the formation of non-caseating epithelioid granulomas in the affected organs⁽⁶⁾. The epidemiological and clinical heterogeneity of this condition, with vast variability depending on demographic parameters such as geographic region, gender, race, and age, suggesting a multiple etiology. The incidence of sarcoidosis ranges from 0.47 to 5 per 100,000 per year in Asian countries (South Korea, Taiwan, Malaysia, Japan) to a peak of

11.3 to 14.8 per 100,000 per year in Scandinavian countries. While sarcoidosis can be diagnosed at any age, the apparent peak incidence is in the range of 46 to 51 years⁽⁷⁾. Although a predominance of involvement in the female sex has been reported, the reason for this is not known⁽⁸⁾. Race influences the prognosis of the disease, being favorable in Caucasians who are most commonly symptomatic and present with erythema nodosum, while African Americans have more severe forms with more frequent extrapulmonary involvement and a more reserved prognosis⁽⁹⁾.

The etiology of sarcoidosis, although remaining unknown, has taken into account a series of environmental factors, considering the histopathological similarity between sarcoid granulomas and those produced by mycobacteria and fungi. Additionally, the seasonal onset with a predominance in spring, clustering of cases in various geographical, professional, and familial environments, and the isolation of infectious agents from biological products of patients with sarcoidosis have been considered⁽⁹⁾. Therefore, a hypothesis to be studied is the role of infection in the pathogenesis of the disease, with the most studied potentially causative transmissible agents being *Mycobacterium tuberculosis*, *Cutibacterium acnes*, *Cutibacterium granulosum* and *Aspergillus nidulans*. Other environmental factors that may represent the starting point of sarcoidosis pathogenesis include pine trees, clayey soil, zirconium, aluminum, and talcum powder⁽¹⁰⁾. The phenotypic heterogeneity of sarcoidosis can be thus caused by the complex interplay of environmental factors in genetically predisposed individuals, with subsequent inflammation leading to the formation of non-caseating granulomas, tending to coalesce and resulting in nodules of a few millimeters⁽¹¹⁾. The WASOG (World Association for Sarcoidosis and Other Granulomatosis) definition criteria include the presence of a clinically and radiologically compatible picture, the identification of non-caseating epithelioid granulomas in biopsy, and the exclusion of other diseases that produce similar histological changes.

Case presentation

We present the case of a 33-year-old male patient, a former smoker with a 30 pack-year history, who quit smoking 12 years ago. He

has no occupational exposure to respiratory hazards but has domestic exposure to antigens, particularly animal proteins. The domestic exposure was permanent to pet fur and droppings, having had a dog and a cat in the environment for the past 7 years. Additionally, he had intermittent exposure to feathers and parrot droppings, providing care for the parrot for approximately 2 weeks per year.

The patient has been known to our department since September 2020 when he presented for pneumological evaluation and the completion of clinical and paraclinical investigations to establish the etiology of the detected lesion polymorphism following a chest computer tomography (CT) conducted in another medical unit.

At the time of the first presentation to our clinic, the patient reported a discreet clinical picture in the respiratory sphere, manifested by inspiratory dyspnea and intermittent thoracic pain located in the anterior chest. During the clinical examination, there were no significant pathological changes. The patient was normoxemic, normotensive, with bilateral present vesicular murmur, without added pulmonary wheezes. However, the patient was underweight, with a body mass index of 17.44 kg/m². Biologically, there were no changes outside the normal range. Serum biochemical parameters, including biochemistry, complete blood count, and coagulogram, showed values within the reference range. Serum angiotensin-converting enzyme was also normal, with a value of 35.88 U/L, but it increased progressively during reassessments (Table 1). Functional respiratory tests, highlighted mild obstructive ventilatory dysfunction, with a maximum expiratory volume per second (FEV1) of 71% of predicted, pulmonary hyperinflation, and a moderately decreased



INTERNAL MEDICINE

Clinical Cases

value of the diffusion capacity through the alveolar-capillary membrane (DLCO), with DLCO at 47.9% of predicted, relatively stable throughout subsequent reassessments (Table 2). The electrocardiogram showed a sinus rhythm without acute repolarization changes.

Chest CT performed in August 2020 revealed mediastinal adenopathies with a tendency to confluence (Figure 1) and bilateral hilar adenopathies (Figure 2), associated with polymorphic lesions in the lung parenchyma, represented by micronodules with a "tree-in-bud" appearance, a pseudonodular pulmonary lesion measuring 11/9 mm in the right Fowler segment (Figure 2), traction bronchiectasis (Figure 3), and bilateral emphysematous bullae (Figure 4). It is worth noting the absence of adenopathies in other locations and the absence of pleural or pericardial fluid accumulations.

Subsequently, dynamic imaging reassessment conducted 3 months after initiating corticosteroid therapy clearly showed a favorable evolution of parenchymal lung lesions (Figure 4 - Figure 5) and near-complete regression of mediastino-hilar adenopathies (Figure 6), remaining stable in subsequent chest CT examinations. It is noteworthy that the infracentimetric character has been maintained, including at the current reassessment, practically around 3 years from the time of diagnosis.

In addition to the CT imaging evaluation, a bronchoscopy was performed, where no visible patent proliferative elements were identified in the accessible territories.

Bronchoalveolar lavage did not provide significant diagnostic contribution, revealing an inflammatory aspect due to the presence of granulocytes at a percentage of 6% (normal values for granulocytes: <3%), with 5% neutrophils (normal values for neutrophils: <3%), and 1% eosinophils (normal values for eosinophils: <0.5%), without other pathological values.

As the etiology of the polymorphic lesions responsible for the patient's symptoms has not been determined despite exhaustive investigations, the next step in the diagnostic process was represented by performing mediastinoscopy.

Therefore, a right station IV lymph node biopsy was performed, with a surgical approach through anterior cervicotomy. Subsequently, the histopathological examination revealed 2 lymph nodes with altered architecture due to the presence of multiple non-necrotizing epithelioid granulomatous nodules, supporting the diagnosis of sarcoidosis.

Combining the results of clinical and paraclinical investigations, the patient was discharged with a diagnosis of mediastino-pulmonary sarcoidosis, stage II radiologically, with a recommendation to initiate systemic

Chronology	Serum angiotensin-converting enzyme level (U/L) Normal range: 13.3 - 63.9 U/L
08.12.2020	35,88
20.04.2021	47,35
24.04.2023	81,07
02.11.2023	97,24

Table 1. Variability of Serum Angiotensin-Converting Enzyme Values

Chronology	Diffusion through the alveolar-capillary membrane DLCO (%)
08.09.2020	47.9
08.12.2020	59.9
20.04.2021	48.4
24.04.2022	48.2
02.11.2023	50

Table 2. Variability of diffusing capacity of the lungs for carbon monoxide

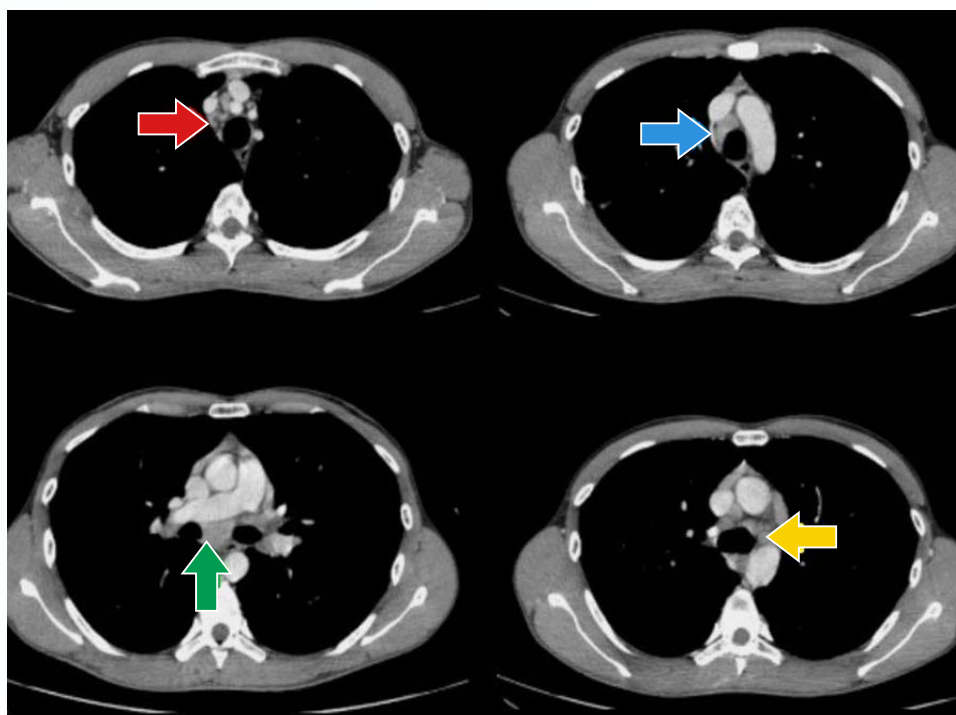


Figure 1. Chest CT August 2020: Red arrow - High mediastinal adenopathies. Blue arrow - Right paratracheal adenopathy. Green arrow - Infracarinal adenopathy. Yellow arrow - Adenopathies in the aortopulmonary window



INTERNAL MEDICINE

Clinical Cases

corticosteroid therapy with Prednisone 30 mg/day, with subsequent gradual de-escalation.

Three months later, the patient returned for pneumological reevaluation. A clear favorable evolution was observed under the recommended treatment, both clinically with almost complete resolution of the symptoms reported at the first admission, and imaging-wise with regression of parenchymal and adenopathic lesions. Furthermore, there was functional improvement with the normalization of lung volumes and a 12% increase in DLCO compared to the previous examination. However, due to the persistence of nonspecific anterior chest pain, a cardio-pulmonary exercise test was recommended to exclude cardiac substrate, a potential angina equivalent. Subsequently, an MRI (Magnetic Resonance Imaging) of the heart with contrast administration was recommended to document a possible cardiac localization of sarcoidosis. Therefore, in the MRI performed over 1 year after establishing the diagnosis of sarcoidosis, a cardioRM aspect suggestive of myocardial involvement was revealed. This was characterized by the presence of a focal fibrotic area in the lateral-apical wall of the left ventricle (Figure 7), with preserved global systolic function and a left ventricular ejection fraction of 60% (Figure 8). Consequently, the background therapy was

supplemented with immunosuppressive treatment - Mycophenolate Mofetil, maintained until August 2022 when an MRI documented the remission of cardiac involvement, with the absence of lesions present in the previous investigation (Figure 9). Relatively recently, approximately 3 years later, the patient continues to show favorable evolution, with clinical and imaging remission (Figure 10).

Discussion

The diagnostic process of sarcoidosis is guided by the clinician's ability to correlate the clinical and paraclinical picture, complemented by evidence of the mentioned granulomatous process in at least one organ/tissue. However, there are situations in which a biopsy may not be necessarily required for diagnosis, notable examples being Löfgren's syndrome, Heerfordt's syndrome, lupus pernio, and asymptomatic bilateral hilar lymphadenopathies⁽¹²⁾.

The clinical presentation varies depending on the localization, with the patient potentially being asymptomatic, having nonspecific general manifestations (fatigue, weight loss, fever, myalgia, night sweats), or having specific symptoms related to the involved organ. The most commonly affected are respiratory and lymphatic systems^(9, 13). Sarcoidosis involvement can lead to

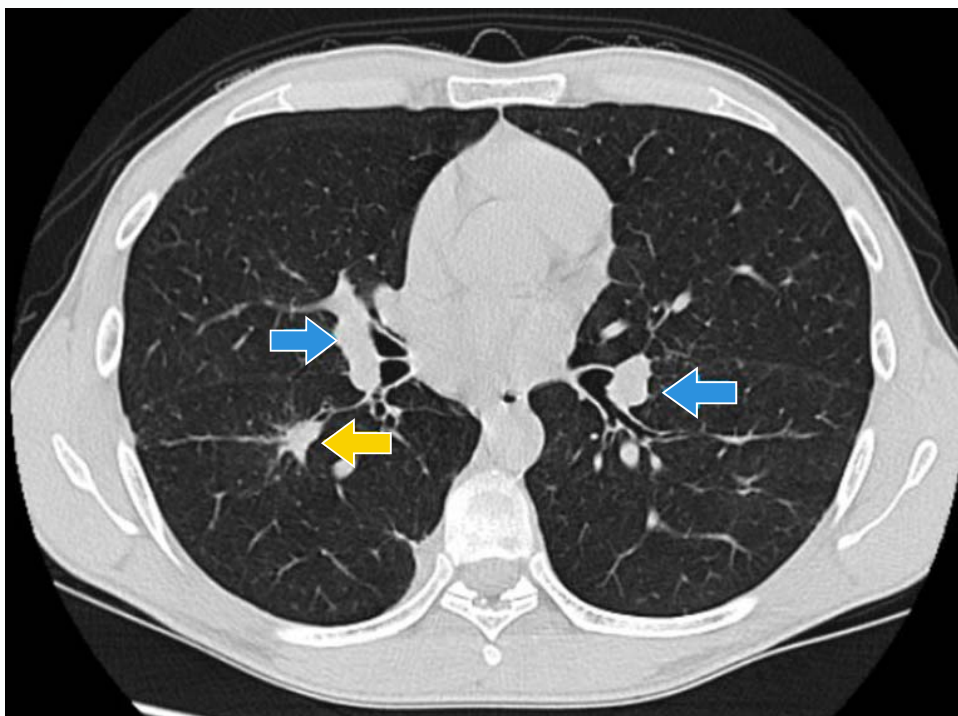


Figure 2. Chest CT August 2020: Blue arrows - Bilateral hilar adenopathies. Yellow arrow - Pseudonodular lesion located in the upper segment of the right lower lobe measuring 11/9mm

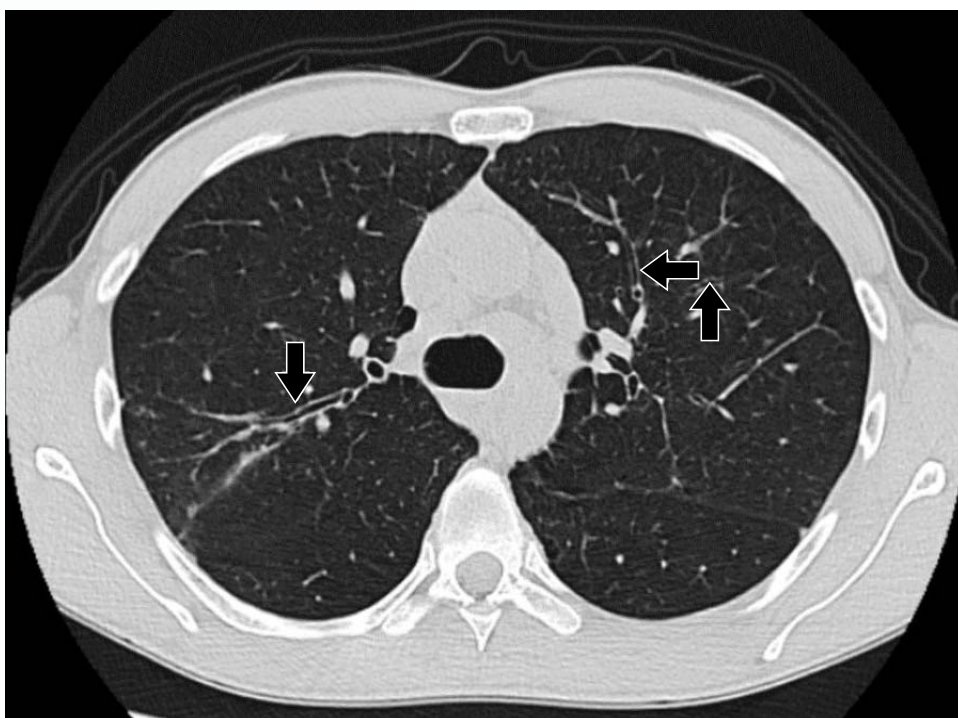


Figure 3. Chest CT August 2020: White arrow - Traction bronchiectasis



INTERNAL MEDICINE

Clinical Cases

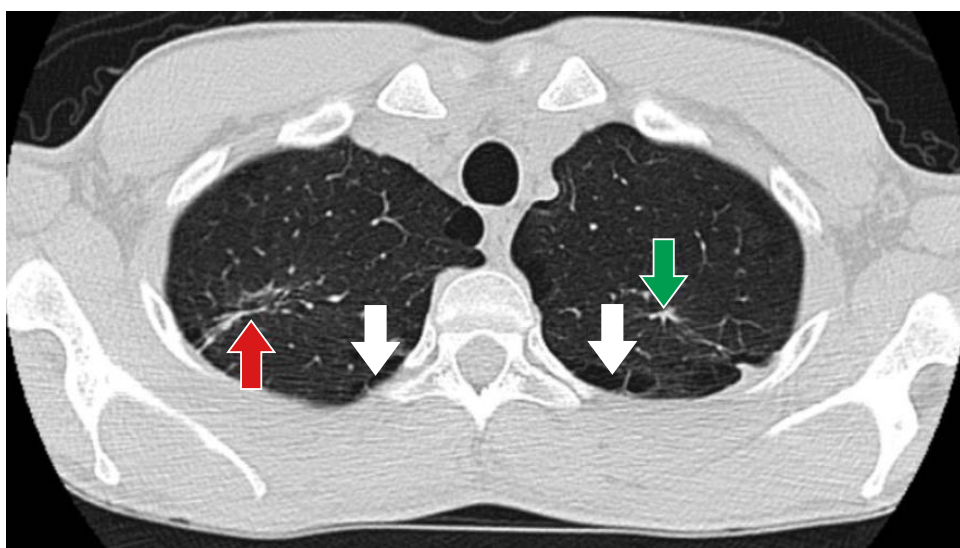


Figure 4. Chest CT August 2020: White arrows - Bilateral emphysematous bullae. Red arrow - Thickened interlobular septa. Green arrow - Stellate-shaped micronodular image measuring 5.5/4.5 mm, left upper lobe



Figure 5. Chest CT December 2020: Favorable evolution

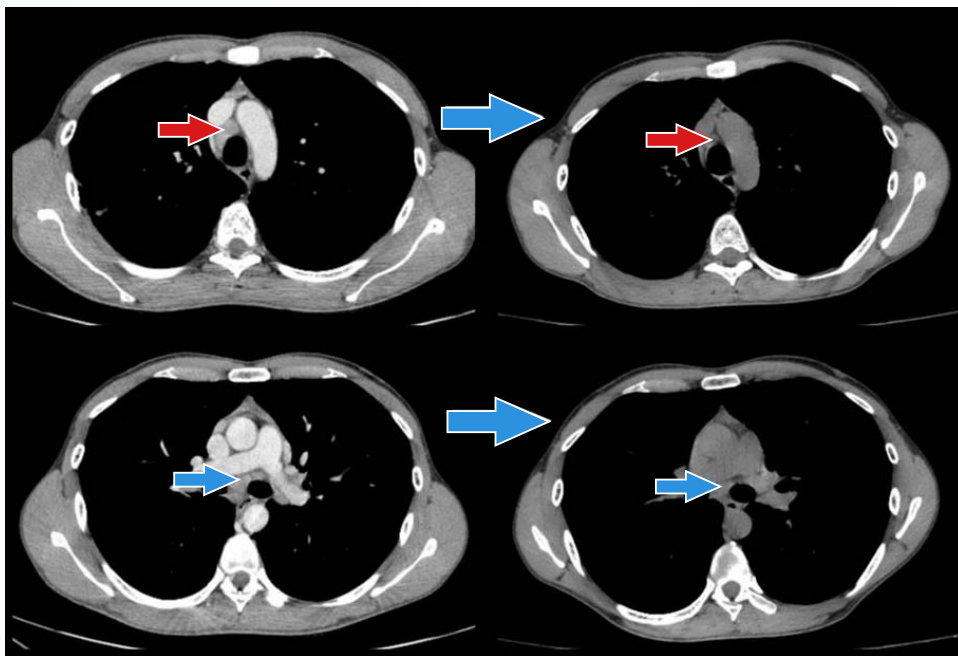


Figure 6. Chest CT August 2020 -> Chest CT December 2020

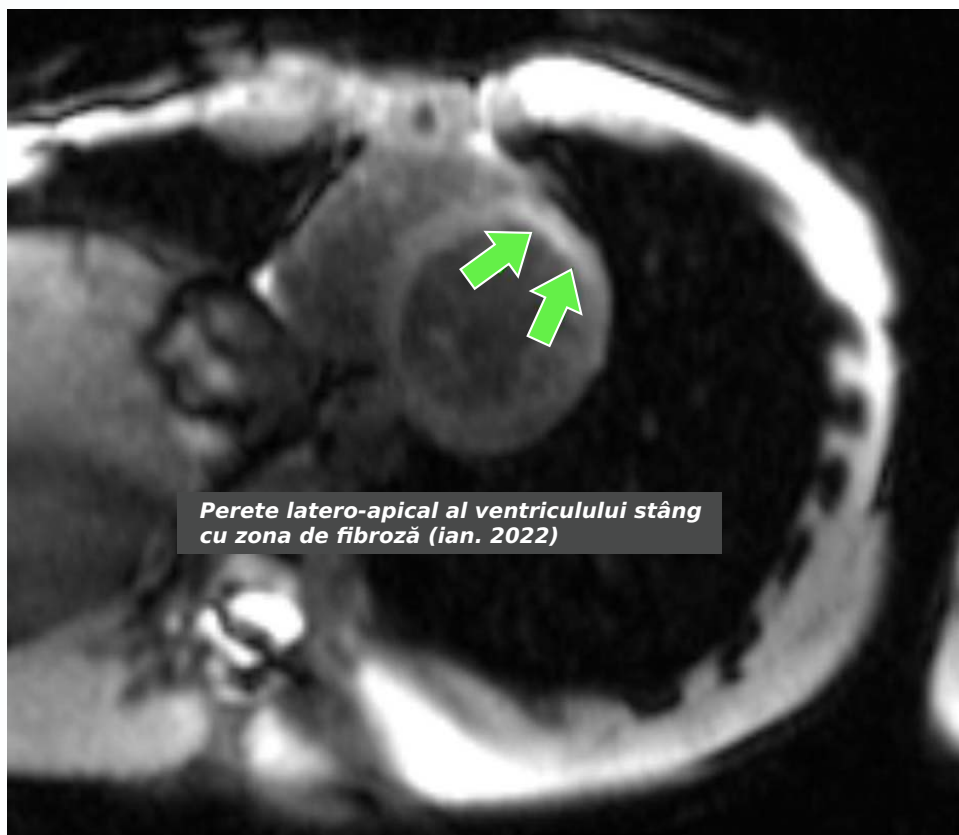


Figure 7. Cardiac MRI January 2022 - Left ventricular lateral-apical wall with an area of fibrosis



INTERNAL MEDICINE

Clinical Cases

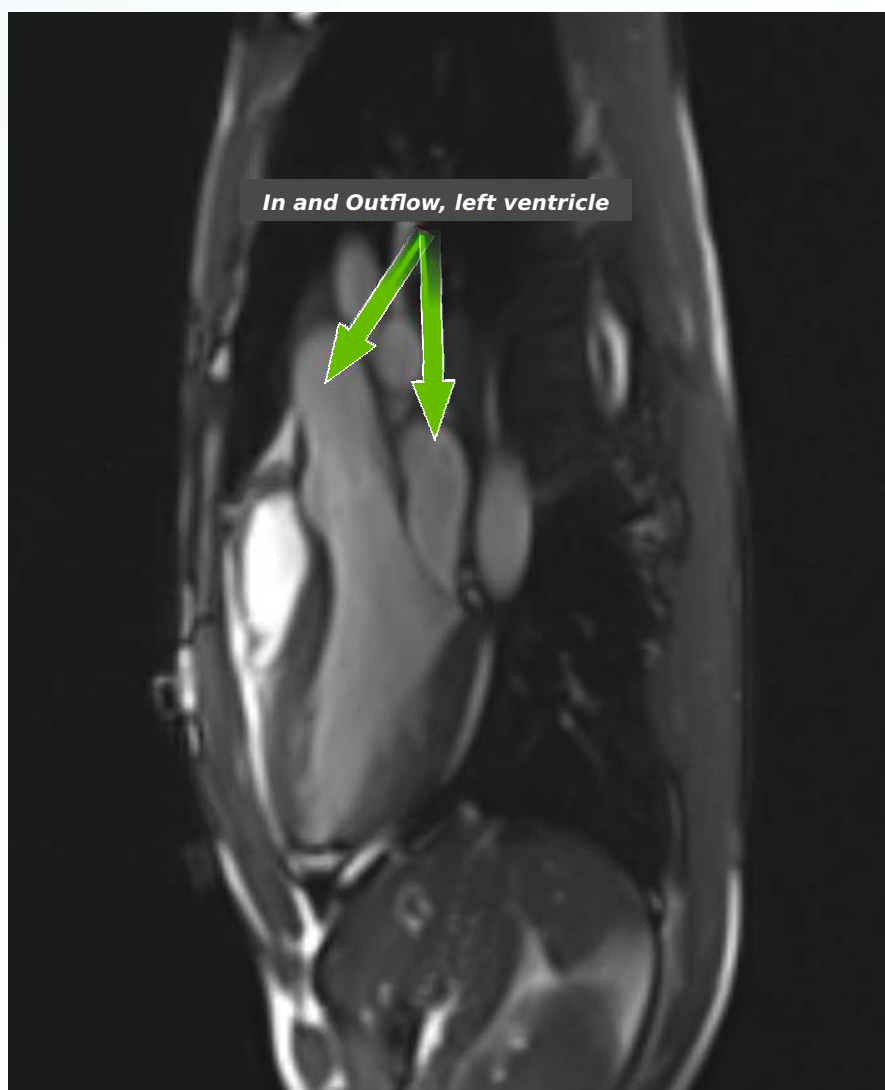


Figure 8. Cardiac MRI January 2022 - Preserved left ventricular ejection fraction

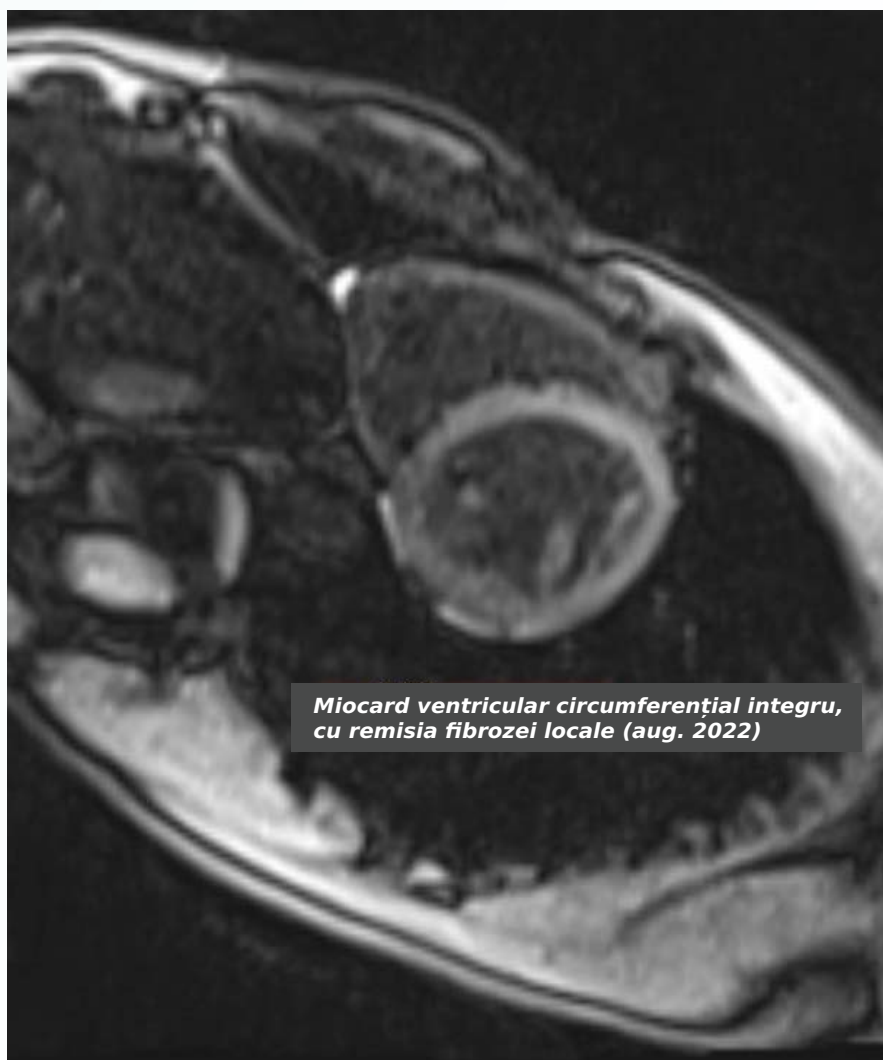


Figure 9. Cardiac MRI August 2022 - Ventricular myocardium circumferentially intact with remission of focal fibrosis

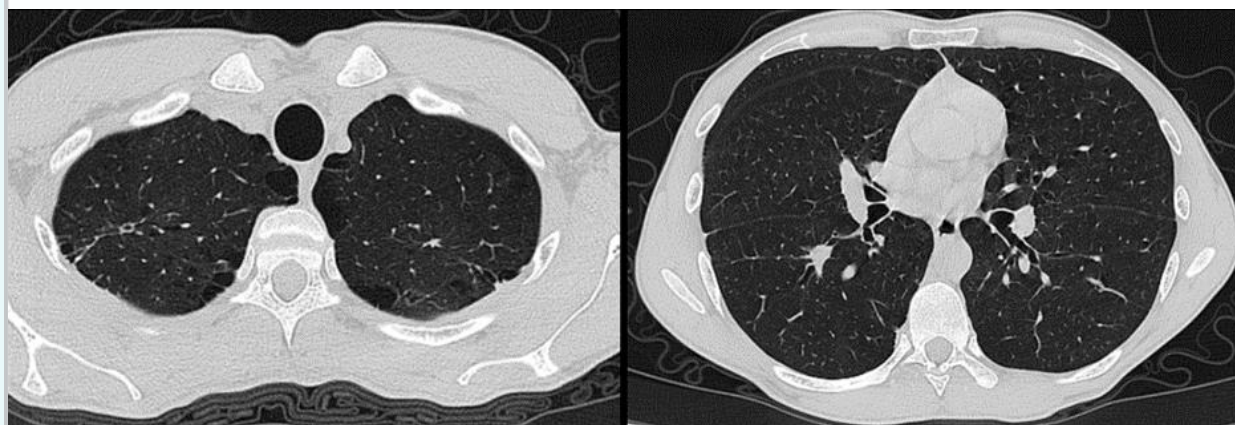


Figure 10. Chest CT November 2023 - No imaging progression on the chest CT reevaluation at 3 years



INTERNAL MEDICINE

Clinical Cases

Radiographic Stage	Radiographic description	Frequency %	Resolution over the subsequent 5 years
0	Normal	5-15	60-90
I	BHL	25-65	60-90
II	BHL + Pulmonary infiltrates	20-40	40-70
III	Pulmonary infiltrates without BHL	10-15	10-20
IV	Pulmonary fibrosis	5	0
BHL: bilateral hilar lymphadenopathy			

Table 3. Radiographic stages at presentation and clinical outcomes⁽¹³⁾

progressive chronic impairment of the affected organs with difficulties in establishing the substrate. Examples in this case include pulmonary hypertension and pulmonary fibrosis, comorbidities that are challenging to differentiate between distinct pathological entities and the inherent complications of the disease⁽⁴⁾.

Pulmonary involvement occurs in 90% of sarcoidosis cases, with patients either being asymptomatic or reporting nonproductive cough, dyspnea, chest pain, or wheezing. Clinical signs are often absent, but occasionally, crackling sounds may be heard on auscultation, or digital clubbing or peripheral cyanosis may be detected.

Pleurisy, chylothorax, or pneumothorax due to the rupture of subpleural emphysematous bullae are very rarely encountered⁽¹³⁾. Based on chest X-ray findings, sarcoidosis is classified into 5 Scadding stages (Table 3). Involvement of the pulmonary parenchyma typically affects the middle and upper thirds of bilateral lung fields. Very rarely, liquid-like opacities may be evident⁽¹³⁾.

Chest CT images typically reveal bilateral symmetrical hilar and mediastinal adenopathies, partially calcified in 50% of cases. Parenchymal lung lesions that may appear include nodular and micronodular opacities distributed bilaterally in a perilymphatic pattern, near the fissures,

peribronchovascular markings, and subpleural areas, with a tendency to confluence (the "Galaxy sign"), sometimes associated with ground-glass opacities.

Bronchoscopic examination through bronchoalveolar lavage is a minimally invasive supportive diagnostic procedure that can contribute to the diagnosis of sarcoidosis in a patient with a suggestive clinical and imaging profile by detecting lymphocytic alveolitis with a predominance of a CD4+/CD8+ T lymphocyte ratio > 3.5. However, it can also reveal opportunistic infections in chronically immunosuppressed patients after long-term corticosteroid therapy (14). A serological parameter with a supportive role in the diagnosis of sarcoidosis is serum angiotensin-converting enzyme (ACE), whose values correlate with the total mass of secreting granulomas, although its specificity is low⁽⁹⁾.

Obtaining a specific histopathological examination for sarcoidosis is most commonly done through transbronchial biopsy of lung parenchyma or affected mediastinal lymph nodes. This reveals aggregates of epithelioid cells without necrosis, surrounded by a few lymphocytes and fibrotic tissue⁽¹⁴⁾.

Clinically silent cardiac involvement in sarcoidosis is estimated at 20-25% of patients, but 5-10% may present with significant arrhythmias or heart failure. For demonstrating myocardial fibrotic involvement, cardiac MRI is considered the gold standard, while PET-CT (Positron Emission Tomography - Computed Tomography) with F-FDG (F-Fludeoxyglucose) is used to highlight myocardial inflammation and guide corticosteroid therapy⁽¹⁵⁾.

A carefully staged and thorough differential diagnosis primarily targets pathological entities such as infections (mycobacteria and

fungi), hypersensitivity pneumonitis, pneumoconiosis, drug toxicity, and autoimmune diseases⁽¹¹⁾.

The therapeutic management of sarcoidosis is determined by the type, localization, and degree of involvement, with oral corticosteroid therapy being the first-line approach, followed by progressive de-escalation. Other treatment options include antifibrotic treatment and lung transplantation in severe cases⁽¹³⁾.

Conclusions

The presented case underscored potential deviations from the clinical and paraclinical characteristics specific to sarcoidosis. Therefore, we have described the progression of a patient with typical chest CT imaging for sarcoidosis, characterized by polymorphic pulmonary lesions and the described adenopathies, with the final diagnosis being established later through mediastinoscopic lymph node biopsy.

The particularity of the discussed case lies in the myocardial involvement, a rare localization of sarcoidosis that required additional and prolonged therapy. Access to high-standard medical investigations, such as cardiac MRI, has made an undeniable contribution to the diagnosis. In cases of suspected cardiac involvement in the context of sarcoidosis, the gold standard remains the typology of late gadolinium enhancement in the affected myocardial area.

The process of accurate diagnosis and well-managed treatment has thus led to favorable outcomes, not only by halting the progression of the disease but also by markedly improving the quality of life, the primary goal of the medical-patient team.

Conflict of interest: *There was no conflict of interest.*



INTERNAL MEDICINE

Clinical Cases

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